REMARKS

Claims 6-13 and 19-43 are pending and are the subject of the present Office Action. The amendments to the specification and claims are illustrated on the attached pages entitled "Marked Up Version to Show Changes Made". For the Examiner's convenience, a clean copy of all the now pending claims 6-13 and 19-43 is provided above.

Each of the objections and rejections set forth in the Office Action are addressed below.

A. Information Disclosure Statement

On December 8, 2000, Applicants filed an Information Disclosure Statement (IDS), Form 1449 and copies of the references cited therein. The Examiner has noted in the Office Action that the references filed in the IDS dated 12-26-00 could not be located. It is assumed that the Examiner is in fact referring to the same IDS as filed by Applicants on December 8, 2000. If this is not correct, the Examiner is asked to please clarify this matter with the undersigned attorney of record.

Applicants are, under separate cover, providing a replacement set of references (originally filed on December 8, 2000) to the Examiner. Since these references are being provided as a replacement to those lost by the Patent Office, it is believed that no fees are due in connection with these references, and that the timing of providing the replacement set of references to the Examiner in no way adversely affects the calculation of patent term on any patent issued for the present application.

B. Objection to Specification

The specification has been amended, pursuant to the Examiner's request, to reflect the status of Applicants' priority application.

C. Section 112 Rejection

Claim 10 was rejected under Section 112, second paragraph, as being indefinite. The subject claim has been amended to correct this

inadvertent, clerical error made when Applicants' filed the response to the restriction requirement electing DR5 agonist antibodies.

D. Obvious-type Double Patenting

Claims 1-10, 19, 25-26, and 28 were rejected as being unpatentable over claims 1-11 and 13-14 of US Patent 6,252,050 in view of Rougier et al. Applicants respectfully traverse this rejection.

First, Applicants wish to clarify that claims 1-5 are no longer pending in the application. The stated rejection accordingly cannot apply to those now cancelled claims, and it is assumed that this is an inadvertent, typographical error in the Office Action. Second, to clarify the actual claims contained in US Patent 6,252,050, only claims 6 and 7 are drawn to "methods". The remaining claims in US Patent 6,252,050 are drawn to compositions of matter, namely, antibody compositions or compositions containing antibodies. Accordingly, the Examiner's statement in the Office Action that "Claims 1-11, 13-14 of US 6,252,050 are drawn to a method of inducing apoptosis in mammalian cancer cells" is not accurate.

It is believed that the claims of the instant application are patentably distinct from the claims of US Patent 6,252,050. The present claims simply do not "combine" two compositions taught by the prior art, as asserted by the Examiner in the Office Action. The present claims are directed to the use of synergistic or effective amounts of anti-DR5 agonist antibody and CPT-11, which Applicants unexpectedly found have a synergistic effect in inducing apoptosis in mammalian cancer cells.

Applicants have amended independent claims 6, 19, 32, 42 and 43 to make even more clear that the amount of agonist anti-DR5 antibody and CPT-11 employed is effective to achieve the synergism in inducing apoptosis in mammalian cancer cells. This amendment is not intended to alter or narrow the scope of the claims as filed; rather it is being made to clarify the synergistic activity of agonist anti-DR5 antibody and CPT-11 discovered by Applicants.

The art does not teach or suggest any reasonable expectation that such agents could be combined to achieve a synergistic effect in

inducing apoptosis in mammalian cancer cells. Even if the skilled artisan would have been motivated by the art to use a combination of anti-DR5 agonist antibody and CPT-11, the only effect that would have reasonably been expected would have been an additive effect. In contrast, Applicants unexpectedly found that the agents act in a synergistic manner such that "the combined effect is greater than the sum of their individual effects." (See, e.g., specification at page 10, lines 16-19). For these reasons, the present claims are not obvious over the cited art.

E. Section 103 Rejections

Claims 6-13 and 19-43 were rejected under Section 103(a) as being unpatentable over US Patent 6,252,050 in view of Rougier et al. Claims 6-13 and 19-43 were also rejected as being unpatentable over WO 98/51793 in view of Rougier et al. The rejections are also respectfully traversed.

As discussed above, certain DR5 antibodies or CPT-11 may have been described in the references cited by the Examiner, but there was no reasonable expectation that such agents could be combined in a certain manner to achieve a synergistic effect in inducing apoptosis in mammalian cancer cells. As provided in the specification, the synergism observed and contemplated in the present invention is such that "the combined effect is greater than the sum of their individual effects." (See, e.g., specification at page 10, lines 16-19). Accordingly, the effect is beyond the additive sum of effects of the respective single agent treatments.

For these reasons, the claimed invention is not obvious over the cited art and withdrawal of the rejections is respectfully requested.

Respectfully submitted,

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In the specification:

On page 1, in the paragraph on lines 7-10, the text has been amended as follows:

---This application is a non-provisional application claiming priority under Section 119(e) to provisional application number 60/138,240 filed June 9, 1999, now abandoned, the contents of which are incorporated herein by reference.---

In the claims:

6. (Twice Amended) A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to [a synergistically effective amount of] agonistic anti-DR5 receptor antibody and CPT-11 in an amount effective to synergistically induce apoptosis in said mammalian cancer cells.

10. (Amended) The method of claim 6 wherein said agonistic anti-[Apo-2 ligand] DR5 receptor antibody is an antibody which cross-reacts with more than one Apo-2 ligand receptor.

19. (Amended) A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to [a synergistically effective amount of] agonistic anti-DR5 receptor antibody and CPT-11 in an amount effective to synergistically induce apoptosis in said mammalian cancer cells, wherein said agonistic anti-DR5 receptor antibody is a monoclonal antibody capable of inducing apoptosis in a mammalian cell expressing DR5 receptor.

32. (Amended) A method of inducing apoptosis in mammalian colon or colorectal cancer cells comprising exposing mammalian colon or colorectal cancer cells to [a synergistically effective amount of] agonistic anti-DR5 receptor antibody and CPT-11 in an amount effective to synergistically induce apoptosis in said mammalian

cancer cells, wherein said agonistic anti-DR5 receptor antibody is a monoclonal antibody capable of inducing apoptosis in a mammalian cell expressing DR5 receptor.

42. (Amended) A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to [a synergistically effective amount of] agonistic anti-DR5 receptor antibody and CPT-11 in an amount effective to synergistically induce apoptosis in said mammalian cancer cells, wherein said agonistic anti-DR5 receptor antibody is a monoclonal antibody capable of inducing apoptosis in a mammalian cell expressing DR5 receptor and binds to the same DR5 receptor epitope to which the anti-DR5 monoclonal secreted by the hybridoma deposited as ATCC accession no. HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534 binds.

43. (Amended) A method of inducing apoptosis in mammalian cancer cells comprising exposing mammalian cancer cells to [a synergistically effective amount of] agonistic anti-DR5 receptor antibody and CPT-11 in an amount effective to synergistically induce apoptosis in said mammalian cancer cells, wherein said agonistic anti-DR5 receptor antibody is a chimeric antibody capable of inducing apoptosis in a mammalian cell expressing DR5 receptor and includes a variable or hypervariable domain of the anti-DR5 monoclonal antibody secreted by the hybridoma deposited as ATCC accession no. HB-12456 or by the hybridoma deposited as ATCC accession no. HB-12534. ---